

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Approved Labeling

Rx only

PRAVIGARDTM PAC

(Buffered Aspirin and Pravastatin Sodium) tablets

(Patient Information leaflet included)

The individual products contained in this package each have additional indications and usage recommendations. For complete prescribing information, consult the package inserts for each individual product.

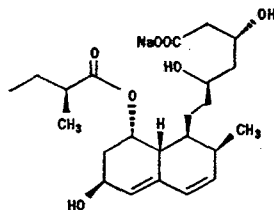
DESCRIPTION

PRAVIGARDTM PAC (Buffered Aspirin and Pravastatin Sodium) is intended to facilitate the daily administration of its individual components, buffered aspirin and PRAVACHOL[®], when used together for the intended patient population (see **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**). PRAVIGARD PAC contains individual daily doses of buffered aspirin 81 mg or 325 mg tablets packed with either PRAVACHOL 20 mg, 40 mg, or 80 mg for oral administration.

PRAVACHOL

PRAVACHOL[®] (pravastatin sodium) is one of a class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, that reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro- β , δ ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1 α (β S*, δ S*),2 α ,6 α ,8 β (R*),8 α]]-. Structural formula:



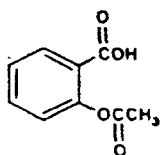
C₂₃H₃₅NaO₇ MW 446.52

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

Pravastatin is available for oral administration in PRAVIGARD PAC at strengths of 20 mg, 40 mg, and 80 mg. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

Buffered Aspirin

The chemical name for aspirin is acetylsalicylic acid and its structural formula is as follows:



Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

Buffered aspirin tablets for oral administration contain 81 mg or 325 mg aspirin as the active ingredient. The formulations are buffered with calcium carbonate, magnesium oxide, and magnesium carbonate. Other ingredients include benzoic acid, citric acid, corn starch, FD&C Blue No. 1, hydroxypropyl methylcellulose, magnesium stearate, mineral oil, polysorbate 20, povidone, propylene glycol, simethicone emulsion, sodium phosphate, sorbitan monolaurate, and titanium dioxide; formulations may also contain carnauba wax and zinc stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

PRAVACHOL

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins (HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

PRAVACHOL produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B – a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for coronary heart disease (CHD). Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with PRAVACHOL reduced Total-C, LDL-C, and apolipoprotein B. PRAVACHOL also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A.

Buffered Aspirin

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A₂. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I₂ (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Buffered Aspirin and Pravastatin Pharmacodynamic Interactions

There is no evidence of a pharmacodynamic effect of aspirin on the lipid lowering effect of pravastatin (see Table 1).

Table 1: Lipid Lowering Effect of Pravastatin With and Without Aspirin				
	Mean Percent Change from Baseline *			
	Total-C	LDL-C	HDL-C	TG
Pravastatin/Aspirin (N=1730)	-22%	-31%	+5%	-11%
Pravastatin/Placebo (N=336)	-21%	-30%	+6%	-9%
Placebo/Aspirin (N=1717)	0%	-1%	+1%	+5%
Placebo/Placebo (N=336)	-1%	-1%	0%	+3%

* On-treatment lipid measures at 3 months from randomization in CARE study.

No study of the effect of pravastatin on the pharmacodynamics of aspirin has been performed.

Pharmacokinetics/Metabolism

PRAVACHOL

Absorption and Distribution

PRAVACHOL (pravastatin sodium) is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior to, meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily

administration of PRAVACHOL tablets. Approximately 50% of the circulating drug is bound to plasma proteins.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation, based on between-subject variability, was 50% to 60% for AUC.

Metabolism and Elimination

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects.

Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3 α -hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω -1 oxidation of the ester side chain, (d) β -oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3 α -hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

Following single dose administration of ¹⁴C-pravastatin, the elimination half-life ($t_{1/2}$) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

Special Populations

Geriatric: In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65 to 75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old). In both studies, C_{max} , T_{max} and $t_{1/2}$ values were similar in older and younger subjects.

Buffered Aspirin

Absorption

In general, immediate-release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see **Pharmacokinetics/Metabolism: Buffered Aspirin: Metabolism**).

Distribution

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, i.e., nonlinear. At low concentrations (<100 micrograms per milliliter [$\mu\text{g/mL}$]), approximately 90% of plasma salicylate is bound to albumin while at higher concentrations (>400 $\mu\text{g/mL}$), only about 75% is bound.

Metabolism

Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 grams [g]), the plasma half-life may be increased to over 20 hours.

Elimination

The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See **OVERDOSAGE: Buffered Aspirin**.) Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, and 10% phenolic and 5% acyl glucuronides of salicylic acid.

PRAVACHOL Co-Administered With Buffered Aspirin

The pharmacokinetic interaction of buffered aspirin (325 mg) and pravastatin (40 mg) were studied in a single-dose crossover study in healthy subjects. Co-administration with buffered aspirin had no significant effect on the C_{max} and AUC of pravastatin. Similarly, co-administration with pravastatin had no significant effect on the C_{max} and AUC of salicylate.

Clinical Studies

PRAVACHOL

Secondary Prevention of Cardiovascular Events

In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)¹ study, the effect of PRAVACHOL, 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either myocardial infarction (MI) (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3-36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had Total-C between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), triglycerides between 35 and 2710 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL significantly reduced the risk for total mortality by reducing coronary death (see Table 2). The risk reduction due to treatment with PRAVACHOL on coronary heart disease (CHD) mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

Table 2: LIPID - Primary and Secondary Endpoints				
Event	Pravastatin 40 mg (N=4512)	Placebo (N=4502)	Risk Reduction (95% CI)	P-value
Primary Endpoint	Number (%) of Subjects			
CHD mortality *	287 (6.4)	373 (8.3)	24% (12, 35)	0.0004
Secondary Endpoints	Number (%) of Subjects			
Total mortality	498 (11.0)	633 (14.1)	23% (13, 31)	<0.0001
CHD mortality or nonfatal MI	557 (12.3)	715 (15.9)	24% (15, 32)	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20% (10, 28)	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19% (0, 34)	0.048
Non-hemorrhagic	154 (3.4)	196 (4.4)	23% (5, 38)	0.015
Cardiovascular mortality	331 (7.3)	433 (9.6)	25% (13, 35)	<0.0001

* The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

In the Cholesterol and Recurrent Events (CARE)² study, the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women)

who had experienced a myocardial infarction in the preceding 3-20 months and who had normal (below the 75th percentile of the general population) plasma Total-C levels. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years and had a mean baseline Total-C of 209 mg/dL. LDL-C levels in this patient population ranged from 101 mg/dL–180 mg/dL (mean 139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total-C, LDL-C, TG, and HDL were -22.0 (-28.4, -14.9), -32.4 (-39.9, -23.7), -11.0 (-26.5, 8.6), and 5.1 (-2.9, 12.7), respectively. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass graft [CABG]), and the risk for stroke or transient ischemic attack (TIA) (see Table 3).

Table 3: CARE - Primary and Secondary Endpoints				
Event	Pravastatin 40 mg (N=2081)	Placebo (N=2078)	Risk Reduction (95% CI)	P-value
Primary Endpoint	Number (%) of Subjects			
CHD mortality or nonfatal MI *	212 (10.2)	274 (13.2)	24% (9, 36)	0.003
Secondary Endpoints	Number (%) of Subjects			
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27% (15, 37)	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26% (4, 44)	0.029

* The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

Primary Hypercholesterolemia (Fredrickson Type IIa and IIb)

PRAVACHOL (pravastatin sodium) is highly effective in reducing Total-C, LDL-C and triglycerides (TG) in patients with heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response is maintained during extended periods of therapy.

A single daily dose is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 mg to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios (see Table 4).

In a pooled analysis of two multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N=277) significantly decreased Total-C, LDL-C, and TG. The 25th and 75th percentile changes from baseline in LDL-C for pravastatin 80 mg were -43% and -30%. The efficacy results of the individual studies were consistent with the pooled data (see Table 4).

Treatment with PRAVACHOL modestly decreased VLDL-C, and PRAVACHOL across all doses produced variable increases in HDL-C (see Table 4).

Table 4: Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration				
Dose	Total-C	LDL-C	HDL-C	TG
Mean Percent Changes From Baseline After 8 Weeks*				
Placebo (N=36)	-3%	-4%	+1%	-4%
10 mg (N=18)	-16%	-22%	+7%	-15%
20 mg (N=19)	-24%	-32%	+2%	-11%
40 mg (N=18)	-25%	-34%	+12%	-24%
Mean Percent Changes From Baseline After 6 Weeks**				
Placebo (N=162)	0%	-1%	-1%	+1%
80 mg (N=277)	-27%	-37%	+3%	-19%

* a multicenter, double-blind, placebo-controlled study

**pooled analysis of 2 multicenter, double-blind, placebo-controlled studies

Buffered Aspirin

Ischemic Stroke and Transient Ischemic Attack (TIA)

In clinical trials of subjects with TIAs due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13-18%.

Prevention of Recurrent MI and Unstable Angina Pectoris

These indications are supported by the results of six large, randomized, multicenter, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects was associated with a significant reduction (about 20%) in the risk of the combination endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients, the event rate was reduced to 5% from the 10% rate in the placebo group.

Chronic Stable Angina Pectoris

In a randomized, multicenter, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34%. The secondary endpoint for vascular events (first occurrence of MI, stroke, or vascular death) was also significantly reduced (32%).

Revascularization Procedures

Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.

PRAVACHOL Co-Administered With Buffered Aspirin

Five PRAVACHOL secondary prevention studies (LIPID, CARE, REGRESS, PLAC I, and PLAC II) were combined in a meta-analysis to assess the independent effects of the concomitant use of pravastatin and aspirin when compared to pravastatin alone and aspirin alone on cardiovascular outcomes.¹⁻⁵ These studies enrolled a total of 14,617 patients who were randomized to receive pravastatin or placebo. Within each randomized group, approximately 20% were not concurrently receiving aspirin. Patients enrolled into these studies included women (15%) and individuals greater than 65 years of age (35%). The independent effects of aspirin and pravastatin on cardiovascular events were seen when the population was grouped according to age and gender. Consistency of these outcomes according to race could not be determined, since information on race was not uniformly collected across all five studies. Baseline histories included previous MI (72%) and revascularization (43%).

Each component of the pravastatin/aspirin combination contributed to the outcome benefits when these benefits were retrospectively defined as:

- the composite endpoint of fatal or nonfatal MI

- the composite outcome of CHD death or nonfatal MI
- ischemic stroke
- the composite outcome of CHD death, nonfatal MI or revascularization procedures
- the composite endpoint of CHD death, nonfatal MI, revascularization procedures or ischemic stroke

Table 5 compares the cardiovascular events seen in subjects receiving the combination of pravastatin/aspirin and aspirin alone, derived from the randomized cohort in the five studies.

Table 5: Number of Events and Risk Reduction of Pravastatin/Aspirin Compared to Aspirin Alone			
Event	Pravastatin/ Aspirin (N=5888)	Placebo/ Aspirin (N=5833)	Risk Reduction (95% CI)
	Number (%) of Subjects		
Fatal or nonfatal MI	445 (7.6)	626 (10.7)	31% (22, 39)
CHD death or nonfatal MI	597 (10.1)	830 (14.2)	31% (23, 38)
Ischemic stroke	134 (2.3)	183 (3.1)	29% (12, 43)
CHD death, nonfatal MI or revascularization procedures	1218 (20.7)	1543 (26.5)	24% (18, 30)
CHD death, nonfatal MI, revascularization procedures or ischemic stroke	1314 (22.3)	1661 (28.5)	24% (19, 30)

Table 6 compares the cardiovascular events seen in subjects receiving the combination of pravastatin/aspirin and pravastatin alone, derived from the non-randomized cohort not receiving aspirin in the five trials.

Table 6: Number of Events and Risk Reduction of Pravastatin/Aspirin Compared to Pravastatin Alone			
Event	Pravastatin/ Aspirin (N=5888)	Pravastatin/ Placebo (N=1436)	Risk Reduction (95% CI)
	Number (%) of Subjects		
Fatal or nonfatal MI	445 (7.6)	125 (8.7)	26% (10, 39)
CHD death or nonfatal MI	597 (10.1)	196 (13.7)	37% (25, 46)
Ischemic stroke	134 (2.3)	44 (3.1)	31% (3, 51)
CHD death, nonfatal MI or revascularization procedures	1218 (20.7)	308 (21.5)	11% (-0.6, 22)
CHD death, nonfatal MI, revascularization procedures or ischemic stroke	1314 (22.3)	341 (23.8)	14% (2, 23)

In a supportive analysis, the effects of pravastatin/aspirin were sustained through five years of follow-up.

INDICATIONS AND USAGE

PRAVIGARD

PRAVIGARD (Buffered Aspirin and Pravastatin Sodium) is indicated in patients for whom treatment with both PRAVACHOL and buffered aspirin is appropriate. As described in the labeling for PRAVACHOL and buffered aspirin below, the components of PRAVIGARD are both indicated to reduce the occurrence of cardiovascular events, including death, myocardial infarction or stroke in patients who have clinical evidence of cardiovascular and/or cerebrovascular disease. Patients receiving treatment with PRAVIGARD should also be placed on a standard cholesterol-lowering diet and should continue on this diet during treatment.

PRAVACHOL

Secondary Prevention of Cardiovascular Events

In patients with clinically evident coronary heart disease, PRAVACHOL (pravastatin sodium) is indicated to:

- reduce the risk of total mortality by reducing coronary death
- reduce the risk of myocardial infarction
- reduce the risk of undergoing myocardial revascularization procedures
- reduce the risk of stroke and stroke/transient ischemic attack (TIA)
- slow the progression of coronary atherosclerosis

Hypercholesterolemia

PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb).

Prior to initiating therapy with PRAVACHOL, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure Total-C, HDL-C, and TG. Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol and Education Program (NCEP - see below) recommends an LDL-C goal of <100 mg/dL in patients who have established CHD or CHD risk equivalents (diabetes, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or multiple risk factors conferring a 10-year risk for CHD >20%).

After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, non-HDL-C (Total-C minus HDL-C) becomes a secondary target of therapy. In patients with CHD or CHD risk equivalents the non-HDL-C goal is <130 mg/dL.

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories			
Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD ^a or CHD risk equivalents (10-year risk >20%)	<100	≥ 100	≥ 130 (100-129: drug optional) ^b
2+ Risk factors (10-year risk $\leq 20\%$)	<130	≥ 130	10-year risk 10%-20%: ≥ 130
			10-year risk <10%: ≥ 160
0-1 Risk factor ^c	<160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

^a CHD, coronary heart disease.

^b Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

^c Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥ 130 mg/dL (see NCEP Guidelines, above).

Buffered Aspirin

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris)

Aspirin is indicated to: (1) reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of

vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft [CABG], Percutaneous Transluminal Coronary Angioplasty [PTCA], and Carotid Endarterectomy)

Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

CONTRAINDICATIONS

PRAVACHOL

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see **WARNINGS: PRAVACHOL: Liver Enzymes**).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see **PRECAUTIONS: Pregnancy: PRAVACHOL**).

Buffered Aspirin

Allergy

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye's Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's Syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

PRAVACHOL

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In three long-term (4.8-5.9 years), placebo-controlled clinical trials, 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than three times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or four times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency ($\leq 1.2\%$) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

It is recommended that liver function tests be performed prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS: PRAVACHOL**). Caution should be exercised when pravastatin is administered to patients who have a recent history of liver disease, have signs that may suggest liver disease (e.g., unexplained transaminase elevations, jaundice), or are heavy users of alcohol (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism: PRAVACHOL**). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS: PRAVACHOL). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus 1 of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see PRECAUTIONS: Drug Interactions: PRAVACHOL). The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Buffered Aspirin

Alcohol Warning

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects

GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

Pregnancy

Pregnant women should only take aspirin if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

PRECAUTIONS

General

PRAVACHOL

PRAVACHOL (pravastatin sodium) may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS: PRAVACHOL**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency

A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 α -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Buffered Aspirin

Renal Failure

Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency

Avoid aspirin in patients with severe hepatic insufficiency.

Sodium-Restricted Diets

Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen, and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Information for Patients: PRAVACHOL Co-Administered With Buffered Aspirin

Patients should be made aware that PRAVIGARD PAC (Buffered Aspirin and Pravastatin Sodium) contains the same ingredient that is in PRAVACHOL (pravastatin sodium) tablets and also contains aspirin.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see **WARNINGS: PRAVACHOL: Skeletal Muscle**). Patients should also be advised to report to their physician any conditions that may increase the risk of bleeding. (See **WARNINGS: Buffered Aspirin: Coagulation Abnormalities and GI Side Effects**. See also **Patient Information** leaflet printed below.)

Drug Interactions

PRAVACHOL

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See **WARNINGS: PRAVACHOL: Skeletal Muscle**.

Cytochrome P450 3A4 Inhibitors: *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors (see *Diltiazem* and *Itraconazole* below). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem: Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole: The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $t_{1/2}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40% to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect.

Warfarin: Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUCs for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max} , and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See **WARNINGS: PRAVACHOL: Skeletal Muscle.**)

In interaction studies with *aspirin*, *antacids* (1 hour prior to PRAVACHOL), *cimetidine*, *nicotinic acid*, or *probucol*, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Buffered Aspirin

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfapyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Endocrine Function

PRAVACHOL

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a $\geq 50\%$ rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity

PRAVACHOL

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

PRAVACHOL

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p < 0.0001$). At these doses, lung adenomas in females were increased ($p = 0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Buffered Aspirin

Administration of aspirin for 68 weeks at 0.5% in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats.

Pregnancy

PRAVACHOL

Pregnancy Category X

See **CONTRAINDICATIONS: PRAVACHOL**.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10X (rabbit) or 120X (rat) the human exposure based on surface area (mg/meter^2). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of

approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Buffered Aspirin

~~Pregnancy Category D~~

See WARNINGS: Buffered Aspirin.

Labor and Delivery

Buffered Aspirin

Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers

PRAVACHOL

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS: PRAVACHOL).

Buffered Aspirin

Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Pediatric Use

PRAVIGARD is not appropriate for use in the pediatric population.



Geriatric Use

PRAVIGARD

Across the five studies (CARE, LIPID, REGRESS, PLAC I, PLAC II) used for the meta-analysis, 35% of subjects were aged 65 and older and 0.8% were aged 75 and older. The number of subjects aged 65 and older in each treatment group was: 1982 (34%) in pravastatin/aspirin, 534 (37%) in pravastatin/placebo, 2017 (35%) in placebo/aspirin, and 534 (37%) in placebo/placebo. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

PRAVIGARD

Across the five studies included in the meta-analysis (CARE, LIPID, REGRESS, PLAC I, PLAC II) the combined use of aspirin and pravastatin (N=5888) was well tolerated and was not associated with any increases in adverse reactions when compared to either pravastatin (N=1436) or aspirin (N=5833) alone. There were no significant differences in adverse reactions between genders or age groups.

PRAVACHOL

Adverse Clinical Events

Short-Term Controlled Trials

Adverse clinical events reported more frequently in pravastatin-treated patients at an incidence greater than 2% in placebo-controlled trials are identified in Table 7.

Table 7: Adverse Events In >2 Percent of Patients Treated With Pravastatin 10-40 mg In Short-Term Placebo-Controlled Trials

Body System/Event	All Events	
	Pravastatin (N=900) % of patients	Placebo (N=411) % of patients
<i>Dermatologic</i>		
Rash	4*	1
<i>Gastrointestinal</i>		
Heartburn	3	2
<i>General</i>		
Fatigue	4	3
Chest Pain	4	2
Influenza	2*	1
<i>Musculoskeletal</i>		
Myalgia	3	1
<i>Nervous System</i>		
Headache	6	4
<i>Respiratory</i>		
Cough	3	2

*Statistically significantly different from placebo

The safety and tolerability of PRAVACHOL at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of PRAVACHOL at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK > 10X ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

In seven randomized double-blind, placebo-controlled trials involving over 21,400 patients treated with 40 mg pravastatin (N=10,764) or placebo (N=10,719), the safety and tolerability in the pravastatin group was comparable to that of the placebo group. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin.

Postmarketing Experience

The following events have been reported rarely during postmarketing experience with PRAVACHOL, regardless of causality assessment:

Musculoskeletal: myopathy, rhabdomyolysis.

Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.

Hypersensitivity: anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.

Dermatologic: a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).

Reproductive: gynecomastia.

Special Senses: vision disturbance including blurred vision and diplopia.

Laboratory Abnormalities: elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

Laboratory Test Abnormalities

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS: PRAVACHOL**).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-C than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: PRAVACHOL: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions: PRAVACHOL**.)

Buffered Aspirin

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See also **WARNINGS: Buffered Aspirin.**)

Gastrointestinal: dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.

Hematologic: prolongation of the prothrombin time.

Hypersensitivity: acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

OVERDOSAGE

PRAVACHOL

To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. (See **WARNINGS: PRAVACHOL.**)

Buffered Aspirin

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. Plasma concentrations of aspirin above 300 µg/mL are clearly toxic. Severe toxic effects are associated with levels about 400 µg/mL. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics/ Metabolism: Buffered Aspirin: Distribution.**) A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms

In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment

Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of

activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

PRAVIGARD

The recommended daily dose of PRAVIGARD is 40 mg of PRAVACHOL with either 81 mg or 325 mg of buffered aspirin. If a daily dose of PRAVACHOL 40 mg does not achieve desired cholesterol levels, 80 mg once daily (with 81 mg or 325 mg of buffered aspirin) is recommended. Some people may require lower doses of PRAVACHOL, and PRAVIGARD is also available with PRAVACHOL 20 mg (see PRAVACHOL below). The daily dose can be taken any time of day, with or without food. Because of the aspirin component, the dose should be taken with a full glass of water, unless the patient is fluid restricted.

PRAVIGARD should be avoided in patients with severe hepatic or renal insufficiency (**PRECAUTIONS: Buffered Aspirin**).

PRAVACHOL

The recommended starting dose is 40 mg once daily. PRAVACHOL can be administered as a single dose at any time of the day, with or without food. The maximal effect of a given dose is seen within 4 weeks. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended.

Lower doses are recommended in some patients. A starting dose of 10 mg daily is recommended in patients with a history of significant renal or hepatic dysfunction. In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done

with caution. The dose of pravastatin generally should not exceed 20 mg/day in those patients receiving concurrent immunosuppressive therapy.

Buffered Aspirin

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted.

Prevention of Recurrent MI or Treatment of Chronic Stable Angina Pectoris: 81 or 325 mg once a day. Continue therapy indefinitely.

Ischemic Stroke and TIA: 81 or 325 mg once a day. Continue therapy indefinitely.

Revascularization Procedures: The maintenance dose following revascularization procedures (CABG, angioplasty, carotid endarterectomy) is 81-325 mg/day of aspirin. Higher doses (to 650 mg/day) have also been recommended post endarterectomy.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.

Carotid Endarterectomy: Doses of 81 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

HOW SUPPLIED

PRAVIGARD™ PAC (Buffered Aspirin and Pravastatin Sodium) Tablets

PRAVIGARD™ PAC is available in cartons containing either 30 buffered aspirin 81 mg or 325 mg tablets packed with either 30 PRAVACHOL (pravastatin sodium) 20 mg, 40 mg, or 80 mg tablets. Within the carton, the buffered aspirin tablets and pravastatin sodium tablets are presented side-by-side each in a separate cavity in a cold-form foil blister card. Each cold-form foil card will contain 5 buffered aspirin tablets and 5 pravastatin sodium tablets, and the carton will contain 6 blister cards.

PRAVACHOL 20 mg tablets are yellow, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 20 engraved on the opposite side.

PRAVACHOL 40 mg tablets are green, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 40 engraved on the opposite side.

PRAVACHOL 80 mg tablets are yellow, oval-shaped, with BMS on one side and 80 on the other side.

The buffered aspirin 81 mg tablets are white, oval, film-coated tablets embossed with a lower-case b on one side. The buffered aspirin 325 mg tablets are white, round, film-coated tablets embossed with a capital B on one side.

PRAVIGARD PAC		
Buffered Aspirin (mg)	PRAVACHOL (mg)	6 Blister Cards of Buffered Aspirin Tablets Co-packaged with PRAVACHOL Tablets
81	20	NDC 0003-5168-11
325	20	NDC 0003-5169-11
81	40	NDC 0003-5173-11
325	40	NDC 0003-5174-11
81	80	NDC 0003-5183-11
325	80	NDC 0003-5184-11

Note: Each card contains 5 buffered aspirin tablets and 5 PRAVACHOL tablets

STORAGE

Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]

REFERENCES

¹The Long-term Intervention with Pravastatin in Ischemic Disease Group. Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels (LIPID). *N Engl J Med* 1998; 339:1349-1357.

²Sacks FM, et al. The Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients with Average Cholesterol Levels (CARE). *N Engl J Med* 1996; 335:1001-9.

³Pitt B, et al. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and Clinical Events. *J Am Coll Cardiol* 1995; 26:1133-9.

⁴Jukema JW, et al. Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Man with Normal to Moderately Elevated Serum Cholesterol Levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; 91:2528-2540.

⁵Crouse JR 3rd, et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC II), *Am J Cardiol* 1995; 75:455-459.

US Patent No.: buffered aspirin 4,664,915

US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

TBD

Issued May 2003

**APPEARS THIS WAY
ON ORIGINAL**

PATIENT INFORMATION

Rx

PRAVIGARDTM PAC (PRAH-vih-gard Pak) (Buffered Aspirin and Pravastatin Sodium) tablets

THIS PRODUCT
CONTAINS ASPIRIN

Read the patient information that comes with PRAVIGARD PAC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information about PRAVIGARD PAC?

- 1) If you have disease in the blood vessels of your heart (coronary artery disease), PRAVIGARD PAC can lower your chances of dying of heart disease, having a heart attack, or having a stroke. PRAVIGARD PAC will only help you while you take it. If you stop taking PRAVIGARD PAC, it will not help you anymore.
- 2) Rarely, patients taking PRAVACHOL (1 of the medicines in PRAVIGARD PAC) have experienced serious muscle damage. It is important that you know the early signs and symptoms of muscle damage. (See "What are the possible side effects of PRAVIGARD PAC?")

What is PRAVIGARD PAC?

PRAVIGARD PAC has 2 medicines in it, buffered aspirin and pravastatin sodium (PRAVACHOL[®]).

Buffered aspirin stops part of the normal blood clotting process and so keeps clots or plugs from forming in your blood vessels. Buffered aspirin has aspirin in it along with other ingredients that may lower your chance of getting an upset stomach.

PRAVACHOL is a prescription medicine that lowers cholesterol in your blood. It lowers your "bad" LDL cholesterol and raises your "good" HDL cholesterol. High cholesterol can lead to plugs or clots in your blood vessels.

PRAVIGARD PAC is for people who may be helped by having their cholesterol lowered and who also have 1 or more of these problems:

- a heart attack in the past
- chest pain from heart problems (also called angina)
- had a bypass operation or angioplasty to open the blood vessels of the heart
- blood flow problems to the brain (such as strokes, near-strokes, or mini-strokes)

You need to follow your doctor's advice and take PRAVIGARD PAC every day for it to lower your chances of dying from your heart disease, having a heart attack, or having a stroke. PRAVIGARD PAC is part of a treatment program that should also include a low-fat diet and exercise. If you stop taking PRAVIGARD PAC, it will not help you anymore. You must tell your doctor if you stop taking PRAVIGARD PAC.

PRAVIGARD PAC should not be used by:

- children younger than 18 years of age
- pregnant women (see below under "**Who should not take PRAVIGARD PAC?**")

Who should not take PRAVIGARD PAC?

Do not take PRAVIGARD PAC if you:

- **have certain liver or kidney problems.** If you have liver or kidney problems, check with your doctor.
- **are pregnant or planning to become pregnant.** PRAVIGARD PAC can reach your baby and may harm it. If you are pregnant, stop taking PRAVIGARD PAC right away and tell your doctor.
- **are breast feeding.** PRAVIGARD PAC can pass into your breast milk and may harm your baby. You may need to choose between breast feeding or taking PRAVIGARD PAC.
- **are 18 years of age or younger.** Children younger than 18 years should not use any product with aspirin in it. Children can get a rare but very serious medical problem called Reye's Syndrome if they take aspirin when they are sick.
- **are allergic to any medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs) or to any of the ingredients in PRAVIGARD PAC.** The active ingredients are PRAVACHOL and buffered aspirin. See the end of this leaflet for a list of all the ingredients in PRAVIGARD PAC. Ask your doctor or pharmacist if you need a list of NSAIDs.

PRAVIGARD PAC may not be right for you or you may need extra care while taking PRAVIGARD PAC. Before you start PRAVIGARD PAC, tell your doctor if you:

- have bleeding problems
- have unexplained muscle aches or weakness
- have stomach problems such as heartburn, upset stomach, stomach pain, or ulcers
- drink 3 or more alcoholic drinks every day
- have asthma (wheezing) along with nasal polyps (small growths in your nose)

Tell your doctor about all of your medical problems or conditions such as a serious injury, a serious infection, or major surgery.

Can PRAVIGARD PAC affect my other medicines?

Tell your doctor about all the medicines you take, including other medicines that contain aspirin, prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines, like

those listed below, can cause serious side effects if you take them while you are taking PRAVIGARD PAC. Be extra sure to tell your doctor if you take any of the following kinds of medicines:

- blood thinners. Blood thinners can increase your chance of bleeding since the aspirin in PRAVIGARD PAC also blocks normal blood clotting.
- certain medicines for high cholesterol or high triglycerides called fibrates

PRAVIGARD PAC may affect how some of your other medicines work. If you take a high blood pressure medicine called an ACE inhibitor, you may need to have your blood pressure checked more often.

How should I take PRAVIGARD PAC?

- Take PRAVIGARD PAC exactly as your doctor prescribes it.
- The usual dose of PRAVIGARD PAC is 1 aspirin tablet with 1 PRAVACHOL tablet once a day. PRAVIGARD PAC comes in different strengths and your doctor may adjust your dose. Do not change your dose without talking to your doctor.
- If you miss a dose, take it as soon as you remember. **Do not** take 2 doses in the same day.
- You can take PRAVIGARD PAC with or without food.
- Take PRAVIGARD PAC with a full glass of water, unless your doctor has told you to keep your fluids low.
- If you take too much PRAVIGARD PAC, call your doctor or Poison Control Center right away.

Some people may need to stop taking PRAVIGARD PAC for a short time. Call your doctor if you plan to have any surgery, medical, or dental procedures. You may be told to stop taking PRAVIGARD PAC for a while to lower your chance of bleeding.

Some people may need to stop taking PRAVIGARD PAC completely, or for a long time (see "What are the possible side effects of PRAVIGARD PAC?").

What activities should I avoid while taking PRAVIGARD PAC?

- Do not get pregnant. If you do, tell your doctor right away.
- Do not breast feed your baby.

What are the possible side effects of PRAVIGARD PAC?

PRAVIGARD PAC contains buffered aspirin and PRAVACHOL. You should be aware of the following serious side effects:

- **Muscle damage:** Rarely, patients taking PRAVACHOL, have experienced serious muscle damage. If you have unexplained muscle pain or weakness while taking PRAVIGARD PAC, **tell your doctor right away.** The following can be signs of serious muscle damage that can lead to kidney damage:
- muscle problems like weakness, tenderness, or pain that don't have a good reason for happening to you

- *a fever or you feel more tired than usual*
- passing brown or dark-colored urine
- **Liver damage:** Rare cases of liver function abnormalities have been reported with PRAVACHOL. Your doctor may do blood tests to check your liver before you start taking PRAVIGARD PAC, and while you take it.
- **Bleeding:** Aspirin can make it harder for your blood to clot. Call your doctor if you have any unusual bleeding.
- **Stomach problems:** Aspirin may cause stomach ulcers or stomach bleeding. Tell your doctor if you get any of the following:
 - heartburn that is new or won't go away
 - nausea or vomiting. Call your doctor right away if you see blood or something that looks like coffee grounds when you vomit.
 - stomach pain that is new or won't go away
 - bowel movements or stools that look like black tar

Allergic reactions: In people who are allergic to aspirin or NSAIDs, aspirin may cause a severe allergic reaction with hives, facial swelling, asthma (wheezing) or shock. Call a doctor or get emergency help right away if you get any of these symptoms.

Common side effects with PRAVIGARD PAC are rash, stomach pain, upset stomach, muscle ache, and headache.

These are not all the possible side effects of PRAVIGARD PAC. For more information, ask your doctor or pharmacist.

Talk to your doctor or pharmacist if you think you have side effects from taking PRAVIGARD PAC.

General information about the safe and effective use of PRAVIGARD PAC.

Do not use PRAVIGARD PAC for a condition for which it was not prescribed. Do not give PRAVIGARD PAC to other people, even if they have the same symptoms that you have. **Keep PRAVIGARD PAC and all other medicines out of the reach of children.** This leaflet summarizes the most important information about PRAVIGARD PAC. If you would like more information talk with your doctor. You can ask your doctor or pharmacist for information about PRAVIGARD PAC that is written for health professionals.

What are the ingredients of PRAVIGARD PAC?

Active Ingredients:

The active ingredient in **buffered aspirin** is aspirin. The active ingredient in **PRAVACHOL** is pravastatin sodium.



Inactive Ingredients:

The inactive ingredients in **buffered aspirin** are calcium carbonate, magnesium oxide, magnesium carbonate, benzoic acid, citric acid, corn starch, FD&C Blue No. 1, hydroxypropyl methylcellulose, magnesium stearate, mineral oil, polysorbate 20, povidone, propylene glycol, simethicone emulsion, sodium phosphate, sorbitan monolaurate, titanium dioxide, carnauba wax, and zinc stearate. The inactive ingredients in **PRAVACHOL** are croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 20 mg tablets and the 80 mg tablets have Yellow Ferric Oxide. The 40 mg tablets have Green Lake Blend (D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

TBD

Issued May 2003